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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/696,686	10/26/2000	Keith D. Allen	3866-4	4566

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EXAMINER

TON, THAIAN N

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 07/05/2002

13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/696,686

Applicant(s)

ALLEN, KEITH D.

Examiner

Thaia N. Ton

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the corresponding address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 April 2002.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-65 is/are pending in the application.
- 4a) Of the above claim(s) 48-52 and 57-65 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-47 and 53-56 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Claims 1-65 are pending.

Claims 1-47 and 53-56 are under current examination.

Election/Restrictions

Applicant's election with traverse of Group I, Claims 1-47 and 53-56 in Paper No. 12 is acknowledged. The traversal is on the ground(s) that Applicants believe a search of all claimed subject matter would not be an undue burden on the Examiner. This is not found persuasive because the claimed subject matter encompasses separate inventions, in particular Groups I-VII. Further, the inventions above have acquired a separate status in the art as a separate subject for inventive effort and require independent searches. The search for each of the above inventions is not co-extensive particularly with regard to the literature search. Further, a reference which would anticipate the invention of one group would not necessarily anticipate or even make obvious another group.

The requirement is still deemed proper and is therefore made FINAL.

Claims 48-52 and 57-65 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention(s), there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 12.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. Particularly, see p. 1, line 14; p. 11, line 7.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Definitions:

[from REVISED INTERIM UTILITY GUIDELINES TRAINING MATERIALS; repeated from <http://www.uspto.gov/web/menu/utility.pdf>]

"Credible Utility" - Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being "wrong". Rather, Office personnel must determine if the assertion of utility is credible (i.e., whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided). An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based is inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the applicant to support the assertion of utility. A *credible* utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use. For example, no perpetual motion machines would be considered to be currently available. However, nucleic acids could be used as probes, chromosome markers, or forensic or diagnostic markers. Therefore, the credibility of such an assertion would not be questioned, although such a use might fail the *specific* and *substantial* tests (see below).

"Specific Utility" - A utility that is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention. For example, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be *specific* in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

"Substantial utility" - a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

B. A method of treating an unspecified disease or condition. (Note, this is in contrast to the general rule that treatments of specific diseases or conditions meet the criteria of 35 U.S.C. 101.)

C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility".

D. A method of making a material that itself has no specific, substantial, and credible utility.

E. A claim to an intermediate product for use in making a final product that has no specific, substantial, and credible utility.

Note that "throw away" utilities do not meet the tests for a *specific* or *substantial* utility. For example, using transgenic mice as snake food is a utility that is neither specific (all mice could function as snake food) nor substantial (using a mouse costing tens of thousands of dollars to produce as snake food is not a "real world" context of use). Similarly, use of any protein as an animal food supplement or a shampoo ingredient are "throw away" utilities that would not pass muster as specific or substantial utilities under 35 U.S.C. ' 101. This analysis should, of course, be tempered by

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consideration of the context and nature of the invention. For example, if a transgenic mouse was generated with the specific provision of an enhanced nutrient profile, and disclosed for use as an animal food, then the test for specific and substantial *asserted* utility would be considered to be met.

"Well established utility" - a specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art. "Well established utility" does not encompass any "throw away" utility that one can dream up for an invention or a nonspecific utility that would apply to virtually every member of a general class of materials, such as proteins or DNA. If this is the case, any product or apparatus, including perpetual motion machines, would have a "well established utility" as landfill, an amusement device, a toy, or a paper weight; any carbon containing molecule would have a "well established utility" as a fuel since it can be burned; any protein would have well established utility as a protein supplement for animal food. This is not the intention of the statute.

See also the MPEP § 2107 - 2107.02.

Claims 1-47 and 53-56 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility, due to its not being supported by either specific and/or substantial utility or a well-established utility.

The specification teaches general uses of the transgenic mice and cells of the claimed invention. Particularly, the specification teaches that the animals, and in particular, mice whose genome comprises a knockout of a TRP gene can be used in methods of identifying agents capable of affecting the phenotype of a knockout mouse [see p. 5, 3rd paragraph], methods for the treatment of bone disease, cartilage disease, or kidney disease, by administration to an appropriate subject, an agent capable of affecting the phenotype of a knockout mouse [see p. 5-6], methods for determining whether expansion of a trinucleotide repeat in a TRP produces a

phenotypic change utilizing knockout stem cells [see p. 6, 3rd paragraph]. The specification further teaches that cells transfected with constructs encoding TRP gene can be used to produce TRP gene products [see pp. 30-31, 33-34]. However, these are non-specific uses that are applicable in general, and not particular to the specific target gene, T243, that is being claimed.

Furthermore, the claimed transgenic cells and animals are not supported by a substantial utility, because no substantial utility has been established for the claimed subject matter. For example, a nucleic acid may be utilized to obtain a protein; the protein could then be used in conducting research to functionally characterize the protein. The need for such research clearly indicates that the protein and/or its function is not disclosed as to a currently available or substantial utility. A starting material that can only be used to produce a final product does not have a substantial asserted utility in those instances where the final product is not supported by a specific and substantial utility. In the instant case, the transgenic cells and animals are final products resulting from processes involving, in particular, the T243 gene, which does not have an asserted or identified specific and substantial utility. The research contemplated by the specification to utilize the claimed transgenic cells or animals in assays to determine phenotypic changes does not constitute a specific and substantial utility. Particularly, because the mechanisms that the T243 is involved in have not been specifically identified by the specification, the above-listed and asserted utilities contemplated by the instant

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specification are neither substantial nor specific, due to being generic in nature.

Note, because the claimed invention is not supported by a specific and substantial utility for the reasons set forth above, credibility has not been assessed.

Claims 1-47 and 53-56 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-47 and 53-56 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed invention is directed to cells, blastocysts, non-human vertebrates and mice comprising a disruption in a target DNA sequence encoding a trinucleotide repeat proteins [TRPs] and methods of identifying agents capable of

affecting the phenotype of a knockout mouse. In further embodiments, the claimed invention is directed to the target DNA sequence T243 or a naturally occurring allelic variation thereof.

The specification teaches that genomic libraries using the lamda ZAP™ system were prepared using mouse embryonic stem [ES] cells to generate pools of phagemid DNA which were screened for specific genes of interest using long-range PCR [see Example 1 and Figure 1]. The products of the PCR reactions were then separated by electrophoresis through agarose gel and then purified using a QIAquick PCR purification kit and vector and fragments were then assembled into constructs. The mouse ES cell library was then prepared from the phage libraries [see Example 2]. The specification teaches that various oligos were amplified and contained both flanking arms for target genes [see Examples 4-11]. Particularly, the specification teaches that identification of flanking DNA for the target T243 gene and the analysis of the resulting homozygous knockout mice [see Example 12]. Individual pools of an R1 ES genomic library were PCR-amplified using oligos SEQ ID NO: 55 and SEQ ID NO: 56 to identify individual wells containing genomic DNA of target T243 as indicated by a 140 bp band and the flanking DNA sequences for target T243 [SEQ ID NO: 50 and 51] were identified. A T243 targeting construct was generated and then linearized and electroporated into mouse ES cells. Upon confirmation of homologous recombination blastocysts were implanted into pseudo-pregnant female mice. The resulting chimeric offspring were then bred to produce

heterozygous T243 mice which were subsequently bred to produce homozygous offspring, which were then analyzed. Daily measurements of the homozygous knockout 243 mice showed that weight gain and growth lengthwise was markedly decreased, when compared with either wild-type or heterozygous littermates [see p. 66 and Figures 9-10]. Further, post-mortem analysis revealed that these homozygous knockout mice had abnormal cartilage and a generalized reduction of bone formation [see p. 66] and dysplastic changes in both kidneys, where the kidneys were small and lacked normal architecture [see p. 67].

Although the specification teaches methods to generate homozygous knockout mice whose genome comprise a knockout in the T243 gene; the specification fails to teach methods of generating any other transgenic animals. Additionally, the specification fails to any relevant teachings or guidance with regard to the production of a transgenic animal as claimed, and one of skill would not be able to rely on the state of the transgenic art for an attempt to produce transgenic non-human vertebrates for the breadth claimed, which comprise a disruption in a gene encoding a TRP. Furthermore, with regard to the claimed breadth of the knockout construct, the specification fails to prepare TRP knockout constructs that would disrupt mammalian genes other than the mouse T243 gene. The specification fails to even provide T243 gene conservation data across different non-human vertebrate species, information that would be necessary for the construction of targeting vectors for use the production of other knockout non-human vertebrates. Note that

the claimed invention is directed to a "disruption" in a gene, which encompasses both the insertion or the deletion in a target gene sequence, and as such, the one of skill in the art would have had to rely upon the unpredictable state of transgenesis to attempt to product the claimed transgenic animals.

However, the art of transgenic animals has for many years stated that the unpredictability lies with the site or sites of integration of the transgene into the target genome. Transgenic animals are regarded to have within their cells cellular mechanisms which prevent expression of the transgene, such as DNA methylation or deletion from the genome (Kappell et al (1992) Current Opinion in Biotechnology 3, 549, col. 2, parag. 2). Mullins et al (1993) states that not all animals express a transgene sufficiently to provide a model for a disease as the integration of a transgene into difference species of animal has been reported to given divergent phenotypes (Mullins et al (1993) Hypertension 22, page 631, col. 1, parag. 1, lines 14-17). The elements of the particular construct used to make transgenic animals are held to be critical, and that they must be designed case by case without general rules to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc. (Houdebine (1994) J. Biotech. 34, page 281). "The position effect" and unidentified control elements also are recognized to cause aberrant expression (Wall (1996) Theriogenology 45, 61, parag. 2, line 9 to page 62, line 3). Mullins et al.(1996) disclose that "the use of nonmurine species for transgenesis will continue to reflect the suitability of a particular species for the specific questions

being addressed, bearing in mind that a given construct may react very differently from one species to another." (Mullins et al (1996) J. Clin. Invest. 98, page S39, Summary). Well-regulated transgenic expression is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues (Cameron (1997) Molec. Biol. 7, page 256, col. 1 -2, bridg. parag.). Factors influencing low expression, or the lack thereof, are not affected by copy number and such effects are seen in lines of transgenic mice made with the same construct (Cameron (1997), Molec. Biol. 7, page 256, lines 3-9). These factors, thus, are copy number independent and integration site dependent, emphasizing the role the integration site plays on expression of the transgene (Cameron (1997), Molec. Biol. 7, page 256, lines 10-13). Further, Sigmund (2000) states that the random nature of transgene insertion, resulting founder mice can contain the transgene at a different chromosomal site, and that the position of the transgene affects expression, and thus the observed phenotype (Sigmund (2000) Arterioscler. Throm. Vasc. Biol. 20, page 1426, col. 1, parag. 1, lines 1-7). With regard to the importance of promoter selection, Niemann (1997) states that transgenic pigs made with different promoters regulating expression of a growth hormone gene give disparate phenotypes - one deleterious to the pig, the other compatible with pig health (Niemann (1997) Transg. Res. 7, page 73, col. 2, parag. 2, line 12 to page 73, col. 1, line 4). While, the intent is not to say that transgenic animals of a particular phenotype can never be made, the intent is to provide art taught reasoning as to

why the instant claims are not enabled. Given such species differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification for any transgenic non-human vertebrate whose genome comprises a disruption in a gene encoding a TRP, other than the exemplified transgenic mouse whose genome comprises a knockout in the T243 gene, it would have required undue experimentation to predict the results achieved in any one host animal comprising a disruption in a gene encoding a TRP, the levels of the transgene product, the consequences of that product, and therefore, the resulting phenotype.

Furthermore, with particular regard to the unpredictable state of the transgenic knockout art, it is noted that disruption of a different exon of the same gene may not result in the anticipated phenotype. See Moreadith et al. (Journal of Molecular Medicine, 1997) who support phenotypic unpredictability in knockout mice. In particular, Moreadith et al. discuss that gene targeting at a particular loci is unpredictable with respect to the resulting phenotype since often the generation of knockout mice, in many instances, changes the prevailing notions regarding the functions of the encoded proteins. For example, Moreadith et al. report that gene targeting at the endothelin loci led to the creation of mice with Hirschsprung's disease instead of the anticipated phenotype (abnormal control of blood pressure). See page 208, column 2, 2nd paragraph.

Note further that certain embodiments of the claimed invention do not recite a phenotype for the claimed non-human vertebrates or mice comprising disruptions

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in a gene encoding a TRP [see, for example, claims 26-34]. Note that the mere capability to perform gene transfer in a mouse is not enabling because a desired phenotype cannot be predictably achieved by simply introducing transgene constructs of the types recited in the claims. While gene transfer techniques are well developed for a number of species, and in particular, the mouse, methods for achieving the desired level of transgene expression in appropriate tissues are less well established. The introduction of DNA into the mammalian genome can ordinarily be achieved most reliably by microinjection or retrovirus-mediated gene transfer. However, the state of the art for transgenics is unpredictable because the method of gene transfer typically relies on random integration of the transgene construct. Insertional inactivation of endogenous genes and position effects (see Wall, 1996, p. 61, paragraph 3) can dramatically influence the phenotype of the resultant transgenic animal. Integration of the transgene near highly active genes or, alternatively, in a transcriptionally inactive region, can influence its level of expression. Furthermore, expression of the transgene and the effect of transgene expression on the phenotype of the transgenic animal depends upon the particular gene construct used, to an unpredictable extent.

It is further noted that certain embodiments of the claimed invention require the use of embryonic stem cells, particularly for the generation of the claimed transgenic mice. However, the state of the art is such that ES cell technology is generally limited to the mouse system at present, and that only "putative" ES cells

exist for other species (see Moreadith *et al.*, J. Mol. Med., 1997, p. 214, *Summary*). Note that “putative” ES cells lack a demonstration of the cell to give rise to germline tissue or the whole animal, a demonstration which is an art-recognized property of ES cells. Moreadith *et al.* supports this observation as they discuss the historical perspective of mouse ES cells as follows:

“The stage was set one could grow normal, diploid ES cells in culture for multiple passages without loss of the ability to contribute to normal development. Furthermore, the cells contributed to the development of gametes at a high frequency (germline competence) and the haploid genomes of these cells were transmitted to the next generation. Thus, the introduction of mutations in these cells offered the possibility of producing mice with a predetermined genotype.”

Such a demonstration has not been provided by the specification or the prior or post-filing art with regard to the generation of any species of animal ES cells, other than the mouse, which can give rise to the germline tissue of a developing animal. In addition, prior to the time of filing, Mullins *et al.* (*Journal of Clinical Investigation*, 1996) report that “although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated.” (page 1558, column 2, first paragraph). As the claims are drawn to methods involving the manipulation of animal embryonic stem (ES), and particularly since the subject matter of the specification and the claimed invention encompasses the use of such

cells for the generation of a transgenic animal, the state of the art supports that only mouse ES cells were available for use for production of transgenic mice.

This is further supported by Pera *et al.* [**Journal of Cell Science** 113: 5-10 (2000)] who present the generic criteria for pluripotent ES or EG cells [see p. 6, 2nd column] and state that, “Thus far, only mouse EG or ES cells meet these generic criteria. Primate ES cells meet the first three of the four criteria, but not the last. Numerous other candidate mammalian ES cells have been described over the years in domestic and laboratory species, but only in the mouse have all criteria been met rigorously.” [See p. 6, 2nd column, last paragraph].

Accordingly, in view of the quantity of experimentation necessary for the production and use of non-human vertebrates, blastocysts, or cells, for the breadth claimed, comprising a disruption in a gene encoding a trinucleotide repeat [TRP], the lack of direction or guidance, as well as the absence of working examples, provided by the specification the production and use of non-human vertebrates, blastocysts, or cells, for the breadth claimed, comprising a disruption in a gene encoding a trinucleotide repeat [TRP], other than the exemplified T243 knockout mice, the unpredictable and undeveloped state of the art for the production of transgenic knockout non-human vertebrates, particularly with respect to the unpredictable nature of the phenotypic effect and the unpredictability in the ES cell art, and the breadth of the claims encompassing non-human vertebrates, it would have required undue experimentation for one skilled in the art to make and/or use

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the claimed non-human vertebrates, knockout constructs, blastocysts and cells, and methods of using the same.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 2-4, 10-18, 25, 29-47, 54, 56 and 57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2, as written, is incomplete. The claim does not provide a step for disruption of the target DNA sequence. Claims 3, 4, 10-18, 25, 29-47, 54, 56 and 57 depend from claim 2.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 12, 15, 16-18, 20, 22-30, 32-34, 45, 46, 53-55 are rejected under 35 U.S.C. 102(b) as being anticipated by Hodgson *et al.* [Hum. Mol. Genet. 1996, 5: 1875-1885].

The claims are directed to cells comprising a disruption in a target DNA sequence encoding a trinucleotide repeat [TRP] wherein the disruption is produced by obtaining a first sequence homologous to a first region of the target DNA sequence, obtaining a second sequence homologous to a second region of the target DNA sequence, inserting the first and second sequences into a targeting construct, and introducing the targeting construct into a cell to produce a homologous recombinant resulting in a disruption in the target DNA sequence [claims 1-3, 12, 15, 20, 22-25, 53]. In further embodiments, the claimed invention is directed to a non-human vertebrate comprising a heterozygous disruption in a gene encoding a TRP [claims 26-31], a knockout mouse comprising a homozygous disruption in a gene encoding a TRP, wherein the disruption inhibits the production of the wild-type TRP [claims 32-34 and 45], cell lines and tissues derived from the claimed mice [claims 46, 54, 55].

Hodgson *et al.* teach that Huntington disease is caused by expansion of a CAG trinucleotide repeat of exon 1 in the HD gene. The HD gene is highly conserved in evolution and the murine homologue is 90% identical at the amino acid level. Previous studies have found that mice with targeted disruption of both alleles causes embryonic lethality [see p. 1875, 2nd column]. Hodgson *et al.* teach the breeding of yeast artificial chromosome [YAC] transgenic mice expressing human huntingtin with mice heterozygous for a targeted heterozygous for a targeted disruption in the murine huntingtin gene and that viable offspring homozygous for

the disrupted murine Huntington's disease [HD] gene expressing human huntingtin derived from the YAC were generated [see *Abstract*]. To generate the transgenic mice expressing the human HD gene, two previously characterized YACs [YGA2 and 353 G6] were purified and microinjected into pronuclei and implanted into foster mothers. Both of the YACS contain the entire HD gene with 18 CAG repeats [see Figure 1]. These YACS contained five PCR markers that span the entire length of the YACS which were used to identify positive transgenic founder mice [see p. 1876, 2nd column, *Results*]. The resulting transgenic founders were further analyzed by Southern blotting and FISH to detect the presence of the human huntingtin protein [see pp. 1877-1888]. The tissue distribution of YAC and the endogenous murine huntingtin proteins was analyzed [see Figure 5] and subcellular fractionation was performed using cortical tissue from a normal and a transgenic mouse [see p. 1879 and Figure 6]. Further, Hodgson *et al.* teach the rescue of the HD knockout lethal phenotype [see p. 1880]. In particular, YAC transgenic mice were bred to mice heterozygous for the targeted disruption in the mouse HD gene and it was found that the expression of the YAC transgene appeared to be sufficient to induce rescue of embryonic lethality.

Accordingly, Hodgson *et al.* anticipate the claimed invention.

Claims 1, 2, 5, 6, 20, 22, 23, 25-29, 46, 55 are rejected under 35 U.S.C. 102(b) as being anticipated by Lia *et al.* [*Hum. Mol. Gen.*, August 1998, 7:1285-1291].

The claims are directed to cells comprising a disruption in a target DNA sequence encoding a TRP, wherein the disruption is produced by obtaining a first sequence homologous to a first region of the target DNA sequence, obtaining a second sequence homologous to a second region of the target DNA sequence, inserting the first and second sequences into a targeting construct, and introducing the targeting construct into a cell to produce a homologous recombinant resulting in a disruption in the target DNA sequence [claims 1, 2], and in further embodiments, wherein the target DNA sequence comprises CTG trinucleotide repeats [claims 5,6]. The claimed invention is further directed to murine stem cells containing the described construct, and in particular, ES cells [claims 20, 22 and 23], and mice comprising a heterozygous disruption in a gene encoding a TRP [claims 25-29].

Lia *et al.* teach that a CTG repeat in the DM protein kinase gene is responsible for causing myotonic dystrophy [see *Abstract*]. Lia *et al.* describe the generation of transgenic mice containing one copy of the human genomic DNA fragment containing the 59 DMPK and DMAHP genes and 55 CTG [see p. 1286, 1st column, paragraphs 1-2]. Lia *et al.* teach the analysis of tissues from the transgenic mice using semi-quantitative RT-PCR [SP-PCR] [see p. 1286 and Table 1].

Accordingly, Lia *et al.* anticipate the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to Patsy Zimmerman, Patent Analyst, at (703) 305-2758. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-8724.

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP 1600/1630

TNT

Thaian N. Ton
Patent Examiner
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